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Perioperative antibiotic prophylaxis has no effect on time to positivity and proportion of positive samples: a cohort study of 64 *Cutibacterium acnes* bone and joint infections

Anagnostopoulos, Alexia ; Bossard, Daniel Andreas ; Ledergerber, Bruno ; Zingg, Patrick O ; Zinkernagel, Annelies S ; Gerber, Christian ; Achermann, Yvonne

Abstract: If a bone or joint infection is suspected, perioperative antibiotic prophylaxis is frequently withheld until the intraoperative microbiological sampling has been performed. This practice builds upon the hypothesis that perioperative antibiotics could render culture results negative and thus impede tailored antibiotic treatment of infections. We aimed to assess the influence of antibiotic prophylaxis within 30 to 60 minutes before surgery on time to positivity of microbiological samples and proportion of positive samples in *Cutibacterium acnes* bone and joint infections. Patients with at least one positive *C. acnes* sample between January 2005 and December 2015 were included and classified as 'infection' if at least 2 samples were positive, otherwise they were considered a 'contamination'. Kaplan-Meier curves were used to illustrate time to culture positivity. We found 64 cases with a *C. acnes* infection and 46 classified as a *C. acnes* contamination. Application of perioperative prophylaxis significantly differed between the 'infection' and 'contamination' group (72.8% versus 55.8%, $p < 0.001$). Within the 'infection' group, we found no difference in time to positivity between those who had or had not received a perioperative prophylaxis (7.07 days (95% CI 6.4-7.7) vs. 7.11 days (95% CI 6.8-7.5), $p = 0.3$). Also, there was no association between the proportion of sample positivity and the application of perioperative prophylaxis (71.6% versus 65.9%, $p = 0.39$). Since perioperative prophylaxis did not negatively influence the microbiological yield in *C. acnes* infections, routine antibiotic prophylaxis can be routinely given to avoid surgical site infections.

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1 **Perioperative antibiotic prophylaxis has no effect on time to positivity and**
2 **proportion of positive samples: a cohort study of 64 *Cutibacterium acnes* bone**
3 **and joint infections.**

4
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Anagnostopoulos - JCM submission

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37 **ABSTRACT**

38 If a bone or joint infection is suspected, perioperative antibiotic prophylaxis is frequently
39 withheld until the intraoperative microbiological sampling has been performed. This
40 practice builds upon the hypothesis that perioperative antibiotics could render culture
41 results negative and thus impede tailored antibiotic treatment of infections. We aimed to
42 assess the influence of antibiotic prophylaxis within 30 to 60 minutes before surgery on
43 time to positivity of microbiological samples and proportion of positive samples in
44 *Cutibacterium acnes* bone and joint infections. Patients with at least one positive *C.*
45 *acnes* sample between January 2005 and December 2015 were included and classified
46 as 'infection' if at least 2 samples were positive, otherwise they were considered a
47 'contamination'. Kaplan-Meier curves were used to illustrate time to culture positivity.
48 We found 64 cases with a *C. acnes* infection and 46 classified as a *C. acnes*
49 contamination. Application of perioperative prophylaxis significantly differed between the
50 'infection' and 'contamination' group (72.8% versus 55.8%, $p < 0.001$). Within the
51 'infection' group, we found no difference in time to positivity between those who had or
52 had not received a perioperative prophylaxis (7.07 days (95% CI 6.4-7.7) vs. 7.11 days
53 (95% CI 6.8-7.5), $p = 0.3$). Also, there was no association between the proportion of
54 sample positivity and the application of perioperative prophylaxis (71.6% versus 65.9%,
55 $p = 0.39$). Since perioperative prophylaxis did not negatively influence the microbiological
56 yield in *C. acnes* infections, routine antibiotic prophylaxis can be routinely given to avoid
57 surgical site infections.

58

59

60 INTRODUCTION

61 In orthopedic surgery, antimicrobial prophylaxis is routinely given to reduce the risk for
62 surgical site infections and colonization of implanted orthopedic devices (1, 2). It is
63 recommended to give an antibiotic agent with bactericidal effect within a window of 30
64 to 60 minutes prior to skin incision in order to target skin commensal bacteria, such as
65 staphylococci, streptococci, or cutibacteria (2). Despite correctly applied antibiotic
66 prophylaxis, orthopedic bone and joint infections still occur in about 1-10% of cases (3).
67 These orthopedic bone and joint infections are typically caused by microorganisms
68 growing in biofilms. Usually, these biofilms are heterogeneously distributed, which is
69 challenging for an accurate localization of infection for diagnostic sampling (4). Biofilm
70 microorganisms are in a metabolically inactive, non-replicating state which make them
71 tolerant to our immune system and to antibiotics (5). Furthermore, biofilm bacteria are
72 enclosed in a polymeric matrix, which protects them from antimicrobial agents and
73 immune responses; biofilm bacteria are therefore difficult to reach, extract and cultivate
74 (4, 6). All of these factors contribute to the challenge of diagnosing biofilm infections
75 including bones and joint infections. Due to these difficulties, when a bone or joint
76 infection is suspected, and surgical treatment is necessary, application of perioperative
77 antibiotic prophylaxis is oftentimes withheld with the goal of increasing the
78 microbiological yield of positive intraoperative biopsy cultures to identify the pathogen
79 (7-10). Only knowing the causative microorganism of the infection allows a correct
80 tailored longterm antimicrobial treatment

81 However, recent studies (11-15) have shown that exposure to antibiotic agents
82 as perioperative single-shot prophylaxis ahead of the intraoperative microbiological

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sampling is not associated with an increase in culture-negative results. Furthermore, studies claim that perioperative antibiotic prophylaxis is needed in septic orthopedic surgeries since it significantly reduces infection rates (16-18). However, these studies were of small sample size, and the heterogeneity of the infections including both virulent and low-virulent pathogens are major concerns.

C. acnes is a slow growing pathogen, which is often involved in bone and joint infections (19) and is therefore qualified for studying the effect of preoperative antibiotic prophylaxis in orthopedic settings. Since previous studies primarily assessed the influence of preoperative prophylaxis on intraoperative culture results, studies examining the number of positive samples and the time to positivity or confirmation of the infection are lacking.

This study builds upon prior results from a large and homogenous cohort of patients with suspected *C. acnes* bone and joint infections (6). We aimed to assess the effect of preoperative antibiotic prophylaxis on time to positivity of *C. acnes* samples, which is a crucial factor for the physician with regard to further therapeutic management. Furthermore, we evaluated the number of positive samples and the time to confirmation of a *C. acnes* infection in patients with and without perioperative antibiotic prophylaxis.

METHODS

Study population

We retrospectively included patients from the University Hospital Balgrist in Zurich with at least one positive intraoperative sample for *C. acnes*, isolated between January 2005

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106 and December 2015. We excluded patients with no available data on antibiotic
107 prophylaxis at the time of surgery. Since antibiotic treatment might influence the time to
108 positivity of *C. acnes* growth, we also excluded samples from patients who had taken
109 antibiotics for ≥ 24 h within 14 days prior to sample acquisition. The University Hospital
110 Balgrist in Zurich, Switzerland, is an orthopedic clinic specialized in bone and joint
111 infections. Approximately 5000 surgical procedures are annually performed.

112 For clinical and demographic parameters at the time of diagnostic work-up, the patient
113 clinical database of the orthopedic clinic and the prospective database of the infectious
114 diseases consultation service were accessed. Microbiological data were collected using
115 the database of the Institute of medical microbiology, University of Zurich, Zurich,
116 Switzerland.

117 Within the same patient, same hospitalization period, same surgery and same
118 infection site, all samples were clustered as one diagnostic set per patient case,
119 regardless if the sample came back positive or negative. Patients were grouped into the
120 following two groups: 'infection' group if *C. acnes* was detected in at least two different
121 samples within the same patient case and 'contamination' group if there was only one
122 positive sample with *C. acnes*. In order to ensure an accurate allocation to one of the
123 two groups, only cases with three or more analyzable samples were included in this
124 analysis (10, 20).

125 The study was approved by the institutional review board in Zurich, Switzerland
126 (KEK Zurich number 2016-00145).

127

128 **Analysis and statistical methods**

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129 For each sample of a patient diagnostic set, we collected details about the diagnostic
130 method used for detection of *C. acnes*, such as tissue or bone samples, sonication fluid,
131 synovial fluid or wound swab, and Gram staining.

132 We calculated time to positivity of *C. acnes* growth for each positive sample as
133 difference in days between start of microbiological culture and identification of *C. acnes*.
134 Among the 'infection' group, time to positivity was referring to culture positivity of the
135 second positive sample to confirm the infection and account for possible contamination.

136 We analyzed the proportion of positive microbiological samples (ratio of positive
137 samples to the total of all samples taken for each patient) in order to account for the
138 larger number of samples taken if an infection was suspected during surgery. We
139 performed a sensitivity analysis to assess potential associations and systematic
140 distortion of the results by the larger number of samples per patient required to be
141 classified into the 'infection' group. We therefore conducted a Cox proportional hazards
142 regression with robust standard errors, adjusted for the number of samples taken and
143 allowing for clustering of samples within patients.

144 Statistical analysis was performed using Stata 15.0 SE (StataCorp, College
145 Station, TX). We used parametric (Student's t-test) and non-parametric tests (Wilcoxon
146 rank-sum test for continuous variables, Fisher's exact test for categorical variables) to
147 compare variables both on a patient or on a sample level, whichever seemed
148 appropriate.

149 We used Kaplan-Meier curves to illustrate the number of days from the
150 intraoperative sampling to culture positivity both the 'infection' and 'contamination'

151 group. Differences between the times to positivity of both groups were analyzed by
152 using log-rank tests.

153

154 **Microbiological processing**

155 *Diagnostic cultures*

156 All the applied preanalytic and cultivation processes, including the incubation times of
157 10 days, have been previously described in detail (6). Tissue samples were vortexed,
158 homogenized, and incubated on agar plates and thioglycolate broth, yet, bone samples
159 were inoculated in thioglycolate broth only. Explanted hardware was sonicated, and
160 cultivated on agar based media and thioglycolate, as recently published (6). For the
161 sonication samples, a threshold of 50 colony-forming units (CFU)/ml bacteria on agar
162 plates was considered positive.

163

164 *Time to positivity of C. acnes growth*

165 As previously described (6), time to positivity was defined as the time (in days) between
166 the start of microbiological culture and one of the following: 1) *C. acnes* - typical
167 colonies on agar plates, 2) turbidity in thioglycolate broth, or 3) a positive signal in blood
168 culture bottles for which *C. acnes* was subsequently identified on agar plates.

169

170 **RESULTS**

171 **Clinical data and perioperative antibiotic prophylaxis**

172 *Patient level*

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173 A total of 110 patients, predominantly male (69.1%) and with a median age of 58.5
174 years (interquartile range (IQR) 50-68) contributed to overall 550 intraoperative
175 samples, collected between January 2005 and December 2015. Among the most
176 common sample sites were shoulder (N = 72) and hip (N = 25), followed by knee (N =
177 6). In 87.3% patients, a prosthesis (58/110) or another foreign body (38/110) was
178 present. In 64 patients (58.2%), an infection with *C. acnes* was diagnosed, defined as at
179 least two positive samples, while identification of *C. acnes* in only one sample of the
180 remaining 46 patients (41.8%) did not fulfill the criteria of a proven infection and was
181 therefore considered contamination.

182 We analyzed 550 samples, of these 484 (88%) were tissue biopsies (including
183 wound swabs and fluids), 54 (9.8%) sonication fluid from removed implants, and 12
184 (2.2%) bone biopsies. This distribution did not significantly differ between the 'infection'
185 group and the 'contamination' group ($p=0.49$). The mean number of samples taken per
186 patient were 5.3 in the 'infection' group (IQR 4-8) and 4.5 in the 'contamination' group
187 (IQR 3-6). In the 'infection' group, a median of three samples (IQR 2-5) were positive
188 with *C. acnes*. Patient characteristics and sample specifications are shown in Table 1.

189 Out of the 64 patients in the 'infection' group, 44 (68.8%) had not received
190 perioperative prophylaxis until intraoperative biopsies for microbiology had been taken,
191 compared to only 23 (50%) in the 'contamination' group ($p=0.047$). If antibiotic
192 prophylaxis had been applied, it was mostly cefuroxime (83.7%), followed by cefazolin
193 (9.3%) (Table 1). Distribution of infection and antibiotic prophylaxis status on a patient
194 and sample level are illustrated in Fig. 1.

195

196 **Time to sample positivity**

197 A total of 274 out of 550 (49.8%) analyzed samples detected *C. acnes*. Among those,
198 the mean time to culture positivity as defined for each group was significantly shorter in
199 the 228 samples of the 'infection' group (6.04 days, 95% CI 5.71-6.37) as compared to
200 the 46 samples of the 'contamination' group (8.37 days, 95% CI 7.69-9.05, $p<0.001$)
201 (Fig. 2a).

202 In order to investigate the influence of perioperative prophylaxis on cultivation
203 time of *C. acnes* within a comparable group of patients, we assessed the time to sample
204 positivity in the 'infection' group only. Of all 342 samples of the 64 patients in the
205 'infection' group, 72.8% (249/342) were collected in patients who had not been exposed
206 to perioperative prophylaxis as compared to the low percentage of 27.2% (93/342) with
207 prophylaxis exposure (Fig. 1). However, the time to positivity within the 'infection' group
208 did not significantly differ between those samples collected from patients exposed to
209 perioperative prophylaxis (mean 7.07, 95% CI 6.4-7.7) and those not exposed to
210 perioperative prophylaxis (mean 7.11, 95% CI 6.8-7.5) ($p=0.3$) (Fig. 2b). The sensitivity
211 analysis confirmed that this finding was not affected by the total number of samples
212 taken per patient (adjusted Hazard Ratio 0.84 (0.60-1.18), $p=0.31$).

213

214 **Proportion of sample positivity**

215 Perioperative antibiotic prophylaxis could also have an influence on the number of
216 positive samples within a case. Overall, the proportion of sample positivity among all
217 110 patients ('infection' and 'contamination' group combined) was 50.9% (95% CI 45.4-
218 56.5). In the 67/110 patients (60.9%), in which no perioperative prophylaxis had been

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219 applied, the proportion of sample positivity was 54.5% (95% CI 46.8-62.1), while the
220 remaining 43 patients (39.1%) with perioperative prophylaxis had a proportion of sample
221 positivity of 45.5%. There was no significant difference in the proportion of sample
222 positivity between the patients with and without perioperative prophylaxis ($p=0.12$).

223 Among the 64 patients with a proven *C. acnes* infection, the proportion of sample
224 positivity was 69.8% (95% CI 63.8-75.8). Of these 64 patients, 44 (68.8%) had not
225 received perioperative prophylaxis; their proportion of sample positivity was 71.6% (95%
226 CI 64.1-79.1). The remaining 20 patients (31.2%) with perioperative prophylaxis had a
227 proportion of sample positivity of 65.9% (95% CI 55.3-76.5). Hence, in the 'infection'
228 group only, there was no significant difference in the proportion of sample positivity
229 between infection patients with perioperative prophylaxis and those without application
230 of antibiotics before or during surgery ($p=0.39$).

231

232 DISCUSSION

233 This is the first study analyzing the influence of perioperative prophylaxis on time to
234 diagnosis and proportion of positive samples in a homogenous group of bone and joint
235 infections caused by the same pathogen, *C. acnes*. As bone and joint infections are
236 causing significant morbidity for the individual and account for large health care
237 expenses (21), the combination of surgical interventions and targeted biofilm-active
238 antibiotic treatment against the causative pathogen is crucial in order to regain
239 functionality (8). Therefore, the timely microbiological identification is one of the
240 mainstays in treating orthopedic infections. We showed that administering perioperative
241 antibiotic prophylaxis did not affect the time to diagnosis of *C. acnes* infection and

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242 therefore will not prolong the timely identification of pathogen in bone and joint
243 infections. Our findings support the routine administration of perioperative prophylaxis,
244 which has previously shown to significantly lower surgical site infection rates (1, 2, 22).
245 One systematic review (18) found a relative risk reduction of 81% of developing
246 postsurgical wound infections among patients with total hip and knee replacements, if
247 perioperative prophylaxis had been administered correctly. Since hip and knee were
248 also the most common surgical sites in our population, a risk reduction of wound
249 infections to this extent would have major implications on the morbidity of our patients
250 and thus our findings.

251

252 Proportion of positive samples within a diagnostic set in our study population of
253 *C. acnes* infections did not differ between patients with and without perioperative
254 prophylaxis (65.9% versus 68.8%). Bone and joint infections are typically biofilm-
255 associated infections, in which bacteria are protected from antibiotic agents (8). In order
256 to kill biofilm bacteria in the stationary phase, bactericidal antimicrobial substances (23)
257 with a good ability to penetrate the biofilm, such as rifampin are required (8).
258 Cephalosporins, commonly used for perioperative prophylaxis, do not have these
259 characteristics. Since the application of a preoperative single-shot antibiotic prophylaxis
260 is primarily active against planktonic bacteria in the bloodstream and tissue, but is
261 unable to penetrate the biofilm, antibiotic prophylaxis has no effect on culture positivity
262 of intraoperative microbiological samples (13, 15, 24).

263

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264 We recommend the routine administration of antibiotic prophylaxis, even when an
265 *C. acnes* infection is suspected, as the administration of a single shot antibiotic
266 prophylaxis did not affect the intraoperative diagnostic yield. Our recommendation is in
267 line with the American Academy of Orthopedic Surgeons (AAOS) guidelines from 2011
268 (15) as well as with a recently published systematic review (24) assessing the influence
269 of perioperative prophylaxis on culture yield among patients with prosthetic joint
270 infections. The authors of both studies (15, 24) did not find a significant difference
271 between the prophylaxis and the non-prophylaxis group, which would outweigh the risk
272 of a postoperative infectious complication if perioperative prophylaxis was withheld. The
273 recommendation of our study, the AAOS guidelines (15), and the systematic review (24)
274 to routinely apply perioperative prophylaxis is not yet included in the French guidelines
275 for bone and joint infections (9) nor in the IDSA guidelines (10) from 2013, which
276 recommend to withhold antimicrobial prophylaxis when the preoperative risk of a
277 prosthetic joint infection is high based on the results of the history, exams,
278 sedimentation rate, CRP level, and preoperative aspiration.

279

280 The strength of our study is the large homogenous cohort of 64 cases with a
281 proven *C. acnes* bone or joint infection. This is to our knowledge, the largest cohort
282 study to date that is focusing exclusively on this low-virulent and yet very relevant
283 pathogen within the orthopedic context. For our study, we did explicitly not choose a
284 virulent pathogen, such as *Staphylococcus aureus*, since identification of virulent
285 pathogens is often less challenging, even if a short course of antibiotic treatment had
286 been given prior to surgery. A further strength of our study is the novel aspect of our

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287 analysis, including the comparison of time to positivity between different patient groups
288 as well as analysis of the proportion of positive samples within the patient clusters. The
289 long-running microbiological protocols for all bone and joint samples in our cohort
290 secured the comparability of the culture results. A limitation of our study is the
291 retrospective study design, which set certain restrictions in terms of availability of
292 information and comparison to control groups.

293

294 In conclusion, based on to our results in patients with *C. acnes* bone and joint
295 infections, perioperative antibiotic prophylaxis did not influence the intraoperative
296 diagnostic yield of microbiological cultures. We therefore recommend that perioperative
297 antibiotic prophylaxis in elective orthopedic infection operations should be routinely
298 given and not be withheld until all intraoperative biopsies were taken . This will minimize
299 on the one hand the risk of bacterial infection of the surgical field and on the other hand
300 this will protect the newly implanted hardware.

301

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310

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Anagnostopoulos - JCM submission

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- 386

387 **TABLES AND FIGURES**

388 **Table 1.** Clinical characteristics of 64 patients with bone and joint infections caused by
 389 *C. acnes* (≥ 2 positive *C. acnes* samples) and 46 cases with no infection (1 positive *C.*
 390 *acnes* sample).

	Overall N=110 (%)	Infection N=64 (%)	No infection N=46 (%)	<i>p</i> value
Patient characteristics				
Male gender (%)	76 (69.1)	45 (70.3)	31 (67.4)	0.84
Age [years], median (IQR)	58.5 (50-68)	58.5 (47.5-68)	58.5 (51-69)	0.48
Sample site				0.06
Shoulder	72 (65.5)	47 (73.4)	25 (54.4)	
Hip	25 (22.7)	12 (18.8)	13 (28.3)	
Spine	5 (4.6)	4 (6.2)	1 (2.2)	
Knee	6 (5.5)	1 (1.6)	5 (10.9)	
Other	2 (1.7)	0 (0.0)	2 (4.2)	
Sample type				0.38
Tissue and/or bone	79 (71.8)	48 (75.0%)	31 (67.4%)	
Sonication fluid	32 (28.2)	16 (25.0%)	15 (32.6%)	
Number samples, mean (IQR)	5 (3-6)	5.3 (4-8)	4.5 (3-6)	<0.001
Total positive samples per case, median (IQR)	2 (1-4)	3 (2-5)	1	
Presence of foreign body				0.28
Prosthesis	58 (52.7)	31 (48.4)	27 (58.7)	
Other foreign body	38 (34.5)	27 (42.2)	11 (23.9)	

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	Overall N=110 (%)	Infection N=64 (%)	No infection N=46 (%)	<i>p value</i>
Perioperative prophylaxis				
Yes	43 (39.1)	20 (31.2%)	23 (50.0%)	0.05
Prophylaxis agent				
Cefuroxime	36 (32.7)	17 (26.6)	19 (41.3)	0.14
Cefazolin	4 (3.6)	2 (3.1)	2 (4.4)	
Clindamycin	2 (1.8)	0 (0.0)	2 (4.4)	
Vancomycin	1 (0.9)	1 (1.6)	0 (0.0)	

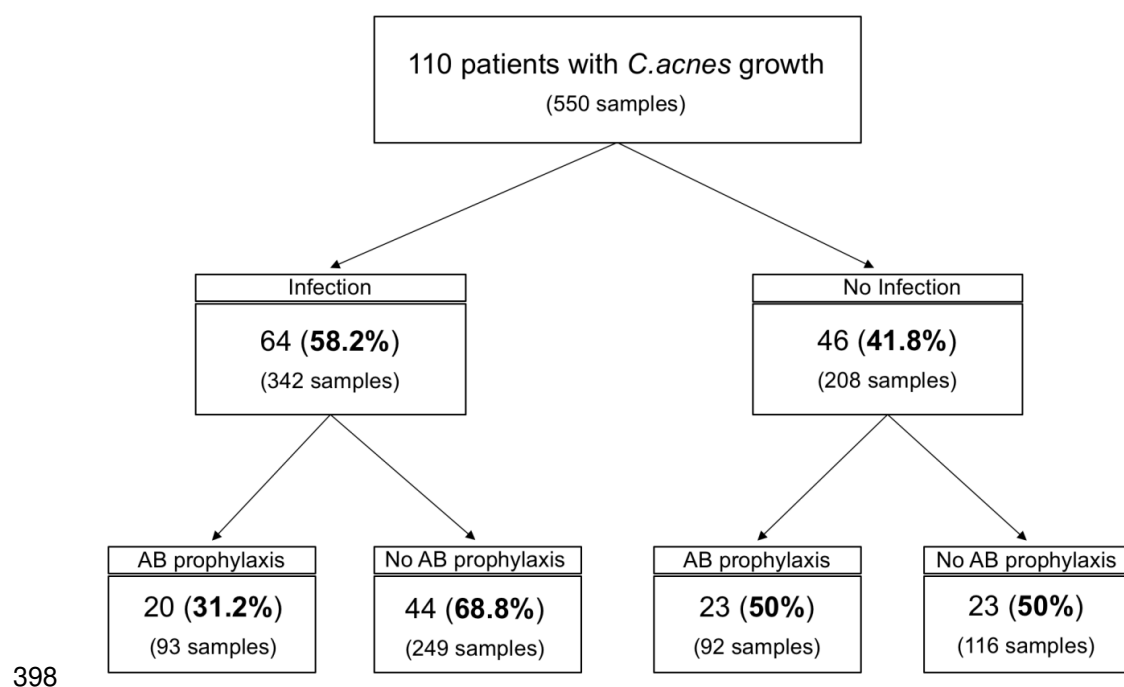
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393 **Fig. 1.** Distribution of infection and preoperative prophylaxis status on a patient and
394 sample level. 68.8% of the patients in the 'infection' group did not receive antibiotic
395 prophylaxis, compared to 50% of patients in the 'contamination' group.

396 Abbreviations: AB, antibiotic

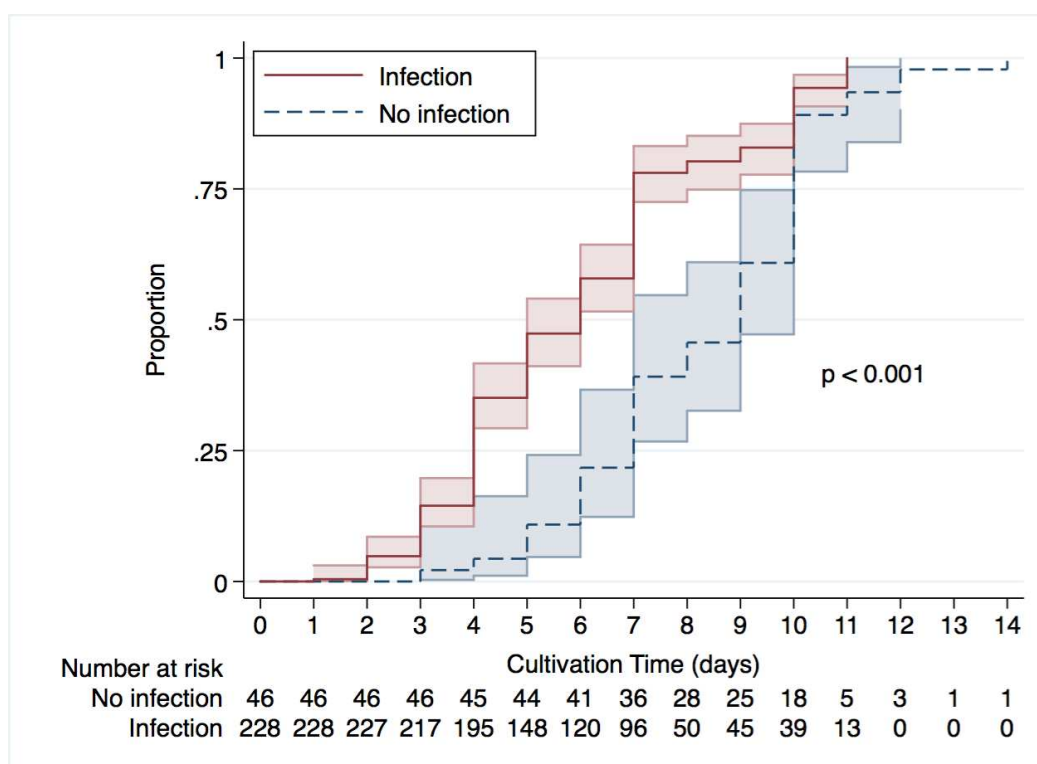
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400 **Fig. 2a.** Kaplan-Meier curve illustrating the proportion of sample positivity with *C. acnes*
401 in all 274 positive samples, stratified by infection status (228 in the 'infection' group vs.
402 46 in the 'contamination' group). The median time to positivity was 6 days for the
403 'infection' group and 9 days for the 'contamination' group (log rank $p < 0.001$). The
404 colored areas represent the 95% confidence interval.

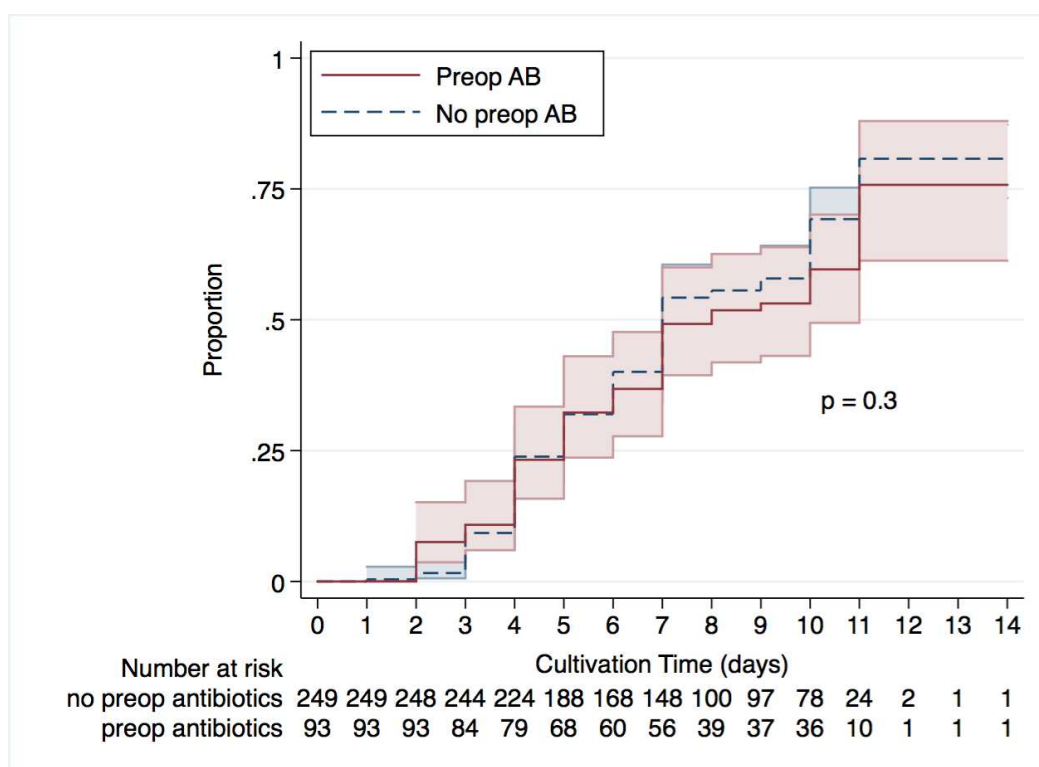


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408 **Fig. 2b.** Kaplan-Meier curve illustrating the proportion of sample positivity with *C. acnes*
 409 in the 342 samples of the 'infection' group, stratified by preoperative prophylaxis (93 in
 410 the 'prophylaxis' group vs. 249 in the 'no prophylaxis' group). The median time to
 411 positivity was 8 days for the 'prophylaxis' group and 7 days for the 'no prophylaxis'
 412 group (log rank $p=0.3$). The colored areas represent the 95% confidence interval.



413

414

415 **FIGURE LEGENDS**

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